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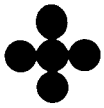

May 18, 1998

Dr. C.W. Jameson
National Institute of Environmental Health Science
79 Alexander Drive
Bldg. 4401 Room 3127
Research Triangle Park, NC 27709

Dear Dr. Jameson:

We write to comment on the recent vote by the NTP's Board of Scientific Counselors to continue to list sodium saccharin (CAS# 128-44-9) as "reasonably anticipated to be a human carcinogen" in the Biennial Report on Carcinogens. We are scientists who have devoted our careers to mechanistic research directed to providing a basis for the interpretation of the results of toxicity studies in animals with regard to their implications for human health. Since a large percentage of positive bioassay tests may in fact not be predictive of a human hazard, especially under realistic exposure conditions, research on mode of action can help to determine the relevance of such studies to human cancer risk.

Most proven human carcinogens are believed to act through DNA-reactive mechanisms. All known human carcinogens that cause bladder cancer are DNA-reactive, involving exposures from cigarette smoking or historically from occupational exposure to genotoxic carcinogens, such as 4-aminobiphenyl or benzidine, in certain industries. In contrast, saccharin is chemically stable and is not DNA-reactive. Accordingly, most genotoxicity tests are negative, although there are some positive results, most of which can be attributed to toxicity. Therefore, saccharin would not be expected to produce cancer in humans according to known mechanisms of bladder carcinogenesis. This literature has been extensively reviewed in a recent publication by Whysner and Williams, in 1996 (Pharmacology & Therapeutics 71:225-252).

A number of physical effects leading to tissue injury have been found to increase the rate of spontaneous tumors normally found in the rat. Examples of this include the presence of bladder calculi and other forms of mechanical irritation, which increase cell proliferation rates. Also included in this category would be the use of cholesterol pellets for delivery systems, such as those used in the early studies of saccharin. Pellet implantation studies with saccharin, and in fact any chemical, have since been shown to be inappropriate for this reason.

Only the sodium salt of saccharin has been found to produce bladder tumors in experimental animals under non-standard bioassay conditions, which involved exposure early in life. The mode of action of sodium saccharin involves mechanical irritation by crystalline material, formed under experimental conditions that have produced an increased incidence of tumors in experimental animals (Cohen et al. Carcinogenesis 16:343-348, 1995). The formation of these crystals requires very high doses of the sodium salt of saccharin, high urinary protein content and a relatively high urinary pH. These factors are present in male rat urine and to a lesser extent in females and mice when sodium saccharin is included in the diet at very high levels. In humans, however, both the dose of saccharin and the urinary protein content are much lower and would not be expected to produce these crystals. Accordingly, sodium saccharin poses no bladder cancer risk through this mechanism.

The case of saccharin is one in which the mode of action for producing tumors in rodent bioassays has been thoroughly studied and is well understood. Progress in the interpretation of animal testing requires that research results receive experienced and thorough evaluation, including consideration of underlying mode of action. In our opinion, sufficient information is available to justify the removal of saccharin from the NTP's Biennial Report. We believe that the review of the safety of saccharin by NTP's Board of Scientific Counselors did not adequately consider the mechanistic information on the species specific effect of saccharin in male rats.

We understand that many of the concerns regarding the safety of saccharin during the review involved the epidemiological data, which are overwhelmingly negative. Data showing a few associations must be treated cautiously, and in fact with suspicion, when so many studies have been done. We know that a certain number of positive associations will occur randomly among the large number of statistical tests performed. We understand that an International Agency for Research on Cancer (IARC) panel met last year and concluded that the epidemiological data did not indicate a relation between saccharin use and human bladder cancer. In the face of the compelling negative epidemiology data and lack of biological plausibility based upon cancer mechanistic data, isolated associations that are not consistent among the various studies should not be given undue credence.

Our conclusion is that the scientific data show that high doses of sodium saccharin produce bladder tumors in male rats by a species-specific mechanism. In addition, the doses that would be expected to be consumed by humans are at least 100-fold lower than those that produce bladder tumors or even precursor lesions in animals. We agree with the votes of the RG1 and RG2 review panels at NTP to delist saccharin, in contrast to the decision of the NTP Board. In response to the NTP's current Federal Register notice calling for public comment concerning listing or removing saccharin from the report on carcinogens, we support the delisting of saccharin and request that the NTP sponsor another external expert scientific review of this issue.

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On behalf of the Committee,

Yours sincerely,
[Redacted]

Gary M. Williams, M.D.
Director
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GMW:jem